unpatentable over Michalovitz *et al.* (*Cell*, 62:671-680, 1991, "Michalovitz 1") in view of Moberg *et al.* (*J. Cell. Biochem.*, 49:208-215, 1992) and Le Gal La Salle *et al.* (*Science*, 259:988-990, 1993). (Office Action, page 2). Applicants traverse for the reasons of record as supplemented below.

Claims 16 and 22 are the only independent claims in the rejected group. Claim 16 recites, *inter alia*, a recombinant adenovirus comprising a nucleic acid selected from the following Markush group:

> (a) nucleic acids encoding a mutated form of p53 which antagonizes wild-type p53-mediated neuronal cell degeneration *in vitro*;
>
> (b) the site for binding of p53 to DNA; and
>
> (c) nucleic acids encoding an antisense RNA which inhibits expression of p53.

In order to render claim 16 (and claims 17, 19, 20, and 21, which depend therefrom) unpatentable, the combination of Michalovitz 1 with Moberg and Le Gal La Salle must teach or disclose every element of the claimed invention. *See* M.P.E.P. § 2142. Moreover, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *See* M.P.E.P. § 2143.01. The mere fact that references can be combined or modified does not render the resulting combination obvious unless the prior art also suggests the desirability of the combination. *Id.*

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According to the Examiner, "Michalovitz et al. [discloses] a nucleic acid that encodes a mutated p53 which inhibits transformation."[1] (Office Action, page 3). This mischaracterizes the reference. Michalovitz 1 describes the effects of a temperature-sensitive mutant p53 protein on rat embryo fibroblast (REF) cells. *See* Abstract ("We now describe the temperature-sensitive behavior of a particular mutant, p53val135."). At the permissive temperature (i.e., 37.5°C), p53val135 transforms REF cells. *See id.* ("It can elicit transformation at 37.5°C."). At the nonpermissive temperature (i.e., 32.5°C), p53val135 behaves "like authentic wt p53." *Id.* In other words, at 32.5°C, p53val135 does not transform REF cells. Instead, like wild-type p53, p53val135, at 32.5°C, suppresses *myc* + *ras*-mediated transformation of REF cells. *See* Michalovitz 1 at 673 ("the inclusion of a p53val135 ***plasmid*** in a *myc* + *ras* transfection greatly eliminated focus formation at 32.5°C." emphasis added). The Examiner ignores the disclosure in Michalovitz 1 that, at 37.5°C, p53val135 increases transformation. *See id.* ("Interestingly, at 37.5°C, p53val135 markedly enhanced *myc* + *ras* transfection . . ..")

[1] Applicants regret that the Examiner has again accused them of making misleading arguments. (*See* Amendment filed February 19, 2003, note 1 and Office Action mailed May 15, 2003, page 2, "Applicants' arguments are not persuasive and are rather misleading because they have ignored the teachings of the Michalovitz that specifically teaches a temperature sensitive p53val123 [sic, p53val135] that suppresses transformation at 32.5 degree celcius [sic, degrees Celcius]." Despite the Examiner's statement, however, Michalovitz 1 discloses only that p53val135 suppresses transformation at *the nonpermissive temperature*, i.e, when it behaves like wild-type p53. Michalovitz 1 in no way teaches or even suggests that *mutant* p53 suppresses transformation. *See* Main Text.

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Michalovitz 1 neither teaches nor suggests that p53val135 or any other mutant p53 "antagonizes wild-type p53-mediated neuronal cell degeneration *in vitro*" as recited by claim 16.[2] Nor does Michalovitz 1 teach or suggest 1) "the site for binding of p53 to DNA" or 2) "nucleic acids encoding an antisense RNA which inhibits expression of p53" as recited by claim 16. Instead, Michalovitz 1 discloses simply that p53val135 behaves like wild-type p53 at 32.5°C, but behaves like mutant p53 at 37.5°C.

With regard to Moberg, the Examiner asserts "contrary to applicants[']arguments, Moberg teaches inhibition of [the] c-myc promoter by wild type p53 and its teaching is that [the] c-myc promoter is responsive to p53 regulation." (Office Action, page 3). As an initial matter, nothing in the Examiner's statement is "contrary to applicants['] arguments." In fact, Applicants stated on page 4 of the Amendment filed February 19, 2003, "Moberg reported that wild-type p53 inhibited transcription from the c-myc promoter." There is no difference between Applicants' statement and the that of the Examiner. However, as Applicants pointed out in the Amendment filed February 19,

[2] The Examiner states, "Applicants[']arguments that nothing in the prior art suggests the desirability of making an oncogenic adenovirus using mutant p53 is not persusasive [sic, persuasive] because the claimed invention is not to any oncogenic adenovirus but to a recombinant virus or adenovirus that comprises a nucleic acid encoding a mutant form of p53 which antagonizes the effects of wild type p53." (Office Action, page 3). First, Applicants note that claim 16 is directed, *inter alia*, to a virus comprising "nucleic acids encoding a mutated form of p53 which antagonizes wild-type p53-mediated neuronal cell degeneration *in vitro*." This is distinctly different from the Examiner's much broader mischaracterization of "a nucleic acid encoding a mutant form of p53 which antagonizes" *any* "effects of wild type p53." Moreover, the references relied on by the Examiner disclose only that mutant p53 is oncogenic (except for p53val135 which at the nonpermissive temperature behaves like wild-type p53). Therefore, one skilled in the art, based on the references of record, would expect that a virus comprising a nucleic acid encoding a mutant p53 protein would be an oncogenic virus. As Applicants stated on page 6 of the Amendment filed February 19, 2003, the Examiner has pointed to no teaching or suggestion that would motivate one to make such a virus.

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2003, Moberg also teaches that *mutant p53 had no effect* on transcription from the c-myc promoter. *See id*. It is mutant p53, not wild-type 53, that is the subject of the instant invention. Applicants do not see, and the Examiner has not explained, why Moberg would motivate anyone to use mutant p53 for anything, when mutant p53 had no effect in his system.

Finally, the Examiner asserts that Le Gal La Salle teaches the "use of adenoviral vectors for transferring [a] gene in[to] brain both in vitro and in vivo." (Office Action, page 3). According to the Examiner, the motivation for combining Michalovitz 1 with Moberg and Le Gal La Salle "was to use p53 mutant for inhibiting expression of wild type p53." *Id*.

But none of these references discloses that mutant p53 inhibits the expression of wild-type p53. As discussed above, Michalovitz 1 reports that, at 32.5°C, a temperature-sensitive p53 mutant inhibits transformation of REF cells by a combination of two oncogenes, *ras* and *myc*. Michalovitz 1 says nothing about the effect of p53val135 on the expression of wild-type p53. Likewise, Moberg reports that wild-type p53 inhibits transcription from the c-myc promoter. Mutant p53 had no effect and Moberg too says nothing about the effect of p53val135 on the expression of wild-type p53. Finally, Le Gal La Salle has nothing to do with either wild-type or mutant p53. Rather Le Gal La Salle simply reports that brain cells can be transfected using adenoviruses. Because the Examiner has provided no reason why one skilled in the art would make the viral vectors claimed in claim 16 (and claims 17, 19, 20, and 21, which depend therefrom), when Michalovitz 1 and Moberg describe perfectly satisfactory

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plasmid constructs, Applicants request the withdrawal of the rejection of these claims under 35 U.S.C. 103(a).

Claim 22 recites a "method for inhibiting toxicity in cultured neuronal cells" using a nucleic acid selected from the Markush group of claim 16. It is clear that neither Michalovitz 1 nor Moberg, nor Le Gal La Salle teaches or suggests that mutant p53, p53 binding sites or antisense p53 RNA might be useful for inhibiting toxicity in cultured nerve cells. As discussed above, Michalovitz 1 discloses that p53val135 transforms fibroblasts at 37.5°C and behaves like wild-type p53 at 32.5°C. Moberg reports that wild-type p53 suppresses transcription from the c-myc promoter, while mutant p53 has no effect. The findings of Le Gal La Salle are unrelated to p53. Because none of the references relied on teach or suggest the claimed method, Applicants request the withdrawal of the rejection of claim 22 (and claims 25-26, which depend therefrom) under 35 U.S.C. § 103(a).

The Claims Are Not Obvious Over the Combination of Levrero with Michalovitz 2, Funk, and Chopp

The Examiner also maintained the rejection of claims 16-20, 22, 23, 25, and 26 under U.S.C. § 103(a) as allegedly being unpatentable over Levrero *et al.* (*Gene*, 101:195-202, 1991) taken with Michalovitz *et al.* (*J. Cell. Biochem.*, 45:22-29, 1991, "Michalovitz 2")[3] and Funk *et al.* (*Mol. Cell. Biol.*, 12:2866-2871, 1992), and further in view of Chopp *et al.* (*Biochem. Biophys. Res. Comm.*, 182:1201-1207, 1992). (Office Action, page 3). Applicants traverse for the reasons of record as supplemented below.

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[3] In making this rejection, the Examiner refers simply to "Michalovitz." However, in the Office Action mailed November 19, 2002, the Examiner relied on two Michalovitz references. For purposes of this response, Applicants assume that he intended to rely on the same two references in the instant Office Action.

As above, claims 16 and 22 are the only independent claims in the rejected group. Claim 16 recites, *inter alia*, a recombinant adenovirus comprising a nucleic acid selected from the following Markush group:

(a) nucleic acids encoding a mutated form of p53 which antagonizes wild-type p53-mediated neuronal cell degeneration *in vitro*;

(b) the site for binding of p53 to DNA; and

(c) nucleic acids encoding an antisense RNA which inhibits expression of p53.

In order to render claim 16 (and claims 17-20, which depend therefrom) unpatentable, the combination of Levrero with Michalovitz 2, Funk, and Chopp must teach or disclose every element of the claimed invention. *See* M.P.E.P. § 2142. Moreover, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *See* M.P.E.P. § 2143.01. The mere fact that references can be combined or modified does not render the resulting combination obvious unless the prior art also suggests the desirability of the combination. *Id.*

Here, Levrero reports that a replication defective adenovirus transfects a variety of cell lines. *See* Abstract ("The recombinant viruses . . . were used to infect a wide spectrum of cells of different origin."); *see also* page 199, Table I. As is the case for Le Gal La Salle (see above), the findings of Levrero are unrelated to p53.

Michalovitz 2 is a review article concerning various mutant p53's. In contrast to Michalovitz 1, Michalovitz 2 does report that a mutant p53 protein may "act[ ] in a

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dominant negative fashion and [ ] effectively block[ ] the function of its wt counterpart." Page 25, left col. However, Michalovitz 2 discloses that p53 mutants of this type are oncogenic. Like Michalovitz 1, Michalovitz 2 neither teaches nor suggests that dominant negative p53 mutants have any effect on wild-type p53-mediated neuronal cell degeneration. Nor has the Examiner pointed to any evidence that one skilled in the art at the time Applicants made their invention would have reasonably expected that, simply because a p53 mutant might act by antagonizing the tumor suppressing activity of wild-type p53, that same mutant protein would antagonize wild-type p53-mediated neuronal cell degeneration.

The Examiner responds that "the claims directed to the vectors do not recite any such limitations." (Office Action, pages 3-4). But, in fact, they do. Claim 16 (and claims 17, 19 and 20, which depend therefrom) specifically requires that, for those viruses comprising a nucleic acid encoding a mutated form of p53, the encoded mutant protein must "antagonize wild-type p53-mediated neuronal cell degeneration *in vitro*." In the absence of a teaching or suggestion that mutant p53 protein can perform this function, one skilled in the art would expect that a virus comprising a nucleic acid encoding a mutant p53 protein would be an oncogenic virus. As Applicants earlier stated, the Examiner has pointed to no teaching or suggestion that would motivate one to make such a virus. *See* Amendment filed February 19, 2003, page 6.

Funk adds nothing to the combination of Levrero and Michalovitz 2. Funk discloses a DNA binding site for p53 protein complexes. *See* Title. According to the Examiner, Funk's disclosure of a binding site identical to SEQ ID NO: 2, renders obvious a virus comprising that binding site. (Office Action, page 4). Funk does not,

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however, teach or suggest that DNA binding sites for p53 protein complexes should be incorporated into viruses. Moreover, the Examiner has pointed to nothing that would motivate one of ordinary skill in the art to make viruses comprising a DNA binding site for p53 as recited by claim 16. In fact, none of the references of record suggest that such viruses would be useful for any purpose. The simple fact that SEQ ID NO: 2 was disclosed by Funk does not render obvious claims to recombinant viruses comprising SEQ ID NO:2.

Finally, the Examiner relies on Chopp. Chopp reports that p53 is expressed in regions of neuronal necrosis after middle cerebral artery occlusion in the rat. *See* Abstract. According to Chopp, "[t]he data suggest that the presence of p53 is associated with cell death and that hsp[heat shock protein]72 may regulate p53 function." *Id*. While this may suggest that hsp72 might be used to antagonize the role, if any, of p53 in neuronal cell death, Chopp neither teaches nor suggests anything regarding mutant p53, p53 binding sites, or p53 antisense RNA.

The Examiner asserts, however:

> [a]gain applicants[']arguments that there is not evidence of record to suggest that p53 mutants or binding sites with effects on oncogenesis would have any effect on wild type p53 on cell death is not persuasive because Michalovitz taught that [a] p53 mutant inhibited transformation and applicants have not provided any evidence why the mutant will not have [an] effect on cell death in view of the results of Michalovitz, Chopp, Funk and Levrero."

(Office Action, page 4).

Applicants reiterate their position regarding the Michalovitz references:

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1. Michalovitz 1 discloses that wild-type p53 (i.e., p53val135 at the nonpermissive temperature) suppresses transformation by a combination of oncogenes entirely unrelated to the instant invention; and
2. Michalovitz 2 discloses that some p53 mutants behave as dominant negative oncogenes;

There is ***no*** teaching in either reference that a p53 mutant ***behaving as a p53 mutant*** inhibits transformation.

Moreover, the Examiner appears to confuse the respective burdens on each party in making a traversing a *prima facie* case of obviousness. In contrast to the Examiner's position, Applicants do not bear the burden of introducing evidence showing "why the mutant will not have [an] effect on cell death in view of the results of Michalovitz, Chopp, Funk and Levrero." Rather, it is the Examiner's burden to introduce evidence showing that one of ordinary skill in the art would reasonably expect success in using mutant p53 protein to antagonize neuronal cell death following ischemia. *See* M.P.E.P. § 2143.01. Here, that evidence is missing. The Examiner simply points (incorrectly) to Michalovitz as evidence that mutant p53 protein suppresses transformation by oncogenes and concludes that, therefore, mutant p53 protein must also suppress neuronal cell death.[4] The art of record provides no connection between these cellular events and cannot support a *prima facie* case of obviousness.

Because none of the references relied on teach or suggest the claimed method, Applicants request the withdrawal of the rejection of claim 16 (and claims 17-20, which

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[4] This conclusion is unjustified even if one were to conclude from Chopp that the expression of wild-type p53 was the cause of neuronal cell death in ischemic brain.

depend therefrom) under 35 U.S.C. § 103(a).

Claim 22 recites a "method of inhibiting toxicity in cultured neuronal cells" using a nucleic acid selected from the Markush group of claim 16. It is clear that neither Levrero nor Michalovitz 2 nor Funk teaches or suggests that mutant p53, p53 binding sites or antisense p53 RNA might be useful for inhibiting toxicity in cultured nerve cells. Applicants again note that Chopp does not disclose that p53 causes neuronal cell death in ischemic brain. *See* Amendment filed February 19, 2003, pages 6-7. Moreover, Chopp does not disclose that antagonizing the effects of p53 would prevent neuronal cell death in ischemic brain. Chopp simply reports that p53 levels are elevated in necrotic brain regions following ischemia. *See* Abstract. Assuming *arguendo* that Chopp would lead one skilled in the art to believe that p53 played any role in neuronal cell death, that role could as readily be either 1) as a cause of cell death or 2) as a protective response to ischemia. In either case, the combination of Levrero, Michalovitz 2, and Funk neither teaches nor suggests that p53 mutants, p53 binding sites, or antisense p53 RNA (regardless of any possible role in blocking transformation) would effectively prevent neuronal cell death. Because none of the references relied on teach or suggest the claimed method, Applicants request the withdrawal of the rejection of claim 22 (and claims 23 25, and 26, which depend therefrom) under 35 U.S.C. § 103(a).

The Claims Are Not Obvious Over the Combination of Smith with Soussi and Chopp

Finally, the Examiner maintains the rejection of claims 22-26 under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 5,087,617 to Smith taken with Soussi *et al.* (*Nucl. Acids Res.*, 16:11384, 1988), and further in view of Chopp. (Office Action, page 4). According to the Examiner, "it would have been obvious for one

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of ordinary skill in the art at the time the claimed invention was made, to modify the method of Smith by administering a p53 antisense oligonucleotide for the expected effect of suppressing p53 activity by inhibition. (*Id.*) Applicants traverse for the reasons of record as supplemented below.

First, Applicants note that the combination of Smith with Soussi and Chopp cannot render claims 25 and 26 obvious. The claims recite, respectively, a vector and a replication defective virus. These elements are absent from the asserted combination of references.

Second, Smith states that "[t]he present inventor has found that antisense p53 oligonucleotides can inhibit the proliferation of *and ultimately kill* primary human leukemic blasts while not producing similar effects on fresh normal bone marrow cells." Col. 6, lines 24-28 (emphasis added). According to Smith, his method may be used to "deplete the bone marrow of malignant cells prior to infusion back into the bone marrow donor." Abstract. Alternatively, antisense oligonucleotides may be administered systemically for anticancer therapy. *See id.*

There simply is no nexus between the methods disclosed by Smith and the methods encompassed by claims 22-26. Smith uses p53 antisense oligonucleotides to inhibit the proliferation of and ultimately kill transformed cells. The claimed methods use p53 antisense oligonucleotide to prevent injured neurons from dying. That is, the end result achieved by Smith is cell death, while the end result achieved by Applicants' methods is prevention of cell death. *See* Smith, col.6, lines 49-55 ("since simple growth inhibition of malignant cells that lasts only during exposure to antisense oligonucleotides would not be adequate for systemic treatment, with respect to this aspect of the

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invention, it is particularly significant that the present inventor has been able to document selective killing of malignant cells.").

Chopp does not provide the required nexus. As noted above, Chopp does not disclose either that p53 causes neuronal cell death in ischemic brain or that antagonizing the activity of p53 would prevent neuronal cell death in ischemic brain. Chopp simply reports that p53 levels are elevated in necrotic brain regions following ischemia. The Examiner has provided no basis for concluding that one of ordinary skill in the art would reasonably believe that Smith's method for using p53 antisense oligonucleotides to *kill* tumor cells could be used to *prevent the death* of ischemic neurons, even assuming that Chopp shows a role for p53 in neuronal cell death.

Lastly, Soussi does not provide the missing nexus. Soussi merely presents the nucleotide sequence of a cDNA encoding rat p53. Despite the Examiner's contrary assertion, Soussi does not render SEQ ID NO:1 obvious simply because this 18 nucleotide sequence is present in the 1627 nucleotide sequence reported by Soussi. There is nothing in Soussi that would lead one of ordinary skill in the art to conclude that SEQ ID NO: 1 has any special utility.

Because none of the references relied on teach or suggest the claimed method, Applicants request the withdrawal of the rejection of claims 22-26 (under 35 U.S.C. § 103(a).

Applicants request that this Response under 37 C.F.R. § 1.116 be entered by the Examiner, placing claims 16-26 in condition for allowance. Furthermore, Applicants submit that the entry of the Response would place the application in better form for appeal, should the Examiner continue to find the pending claims unpatentable.

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In view of the foregoing remarks, Applicants submit that this claimed invention is neither anticipated nor rendered obvious in view of the prior art references cited against this application. Applicants therefore request the entry of this Response, the Examiner's reconsideration and reexamination of the application, and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

M. TODD RANDS Reg No. 46,249

Dated: August 12, 2003

By:_____

FOR: William L. Strauss
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